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Columbus, Ohio 43231

March 11, 2002

Mr. Tom Perez, M.P.H.
Center for Drug Evaluation & Research
Food & Drug Admin., HFD-21
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Perez,

Enclosed herewith is a copy of my "Vita", statement which I intend to make on April 23, 2002 together with significant articles which may not have been read by members of the panel.

You requested copies of this information prior to April 13, 2002.

Sincerely Yours,

William W. Brown

WWB/bp

Enclosures

Resume Of:

WILLIAM W. BROWN

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Columbus, Ohio 43231
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SUMMARY OF CREDENTIALS

- Highly respected member of the central Ohio legal community with 42 years in general practice with extensive trial experience, and estate planning.

- Substantial involvement in the Christian community in areas to include youth leadership, adult education and pastoral search administration. Legal counsel to Association of Christian Schools.

- Successful land and real estate developer with major achievement in direction of survey, platting and sales of 200 acres in Licking County, Ohio.

- Frequent lecturer at seminars for attorneys, banks, certified public accountants, financial planners, insurance agents, and physicians.

LICENSURE

LICENSED PRACTICING ATTORNEY

States of Ohio, Michigan & Kentucky
Supreme Court of United States
Federal District Courts

EDUCATION

M.S. EDUCATIONAL ADMINISTRATION
University of Dayton
Dayton, Ohio
(1982)

JURIS DOCTORATE
Capital University
Columbus, Ohio
(1966)

L.L.B.
Franklin University
Columbus, Ohio
(1960)

BACHELOR OF ARTS
Ohio Wesleyan University
Delaware, Ohio
(1955)

SIGNIFICANT ACCOMPLISHMENTS

LEGAL PRACTITIONER - Forty-two years of achievement in general practice of law relative to estate planning, trusts, wills, probate. Seasoned expertise in plaintiff's trial work to include negligence, products liability, domestic relations, eminent domain. Legal counsel to Association of Christian Schools. Three years with state attorney general's office involved in trial of appropriation cases.

EDUCATIONAL ADMINISTRATION - Diversified leadership skills demonstrated relative to Christian education and administration. Instructional experience to adults on the seminary level to include Bible Institute Courses for Grace Brethren Church, Worthington, Ohio. Worthington Christian High School Instructor in Bible Studies, American History and Civics. Chairman of Pulpit Search Committee and Youth Director for First Baptist Church. Developed and published policy manual for Interdenominational Christian School.

EMPLOYMENT HISTORY

PRIVATE PRACTITIONER
Columbus, Ohio
(1/66 - present)

ASSISTANT ATTORNEY GENERAL
State Ohio - Highway Section
Columbus, Ohio
(1/63 - 1/66)

STAFF ATTORNEY
Fontana, Ward & Kaps
Columbus, Ohio
(9/60 - 1/63)

MEMBERSHIPS

Worthington Hills Country Club
Ohio Bar Association
Columbus Bar Association
National Association of Elder Law Attorneys
Grace Brethren Church of Columbus
Christian Legal Society
AARP Legal Services Network, Certified Estate Planning Attorney

AUTHORSHIPS

1983 Policy Manual for Christian School Boards (200 pages)
1990 Estate Planning: A Practical Guide (850 pages) - published in 1991 by Clark, Boardman and Callaghan (West)
1995 Trusts (600 pages) - published in 1996 by Clark, Boardman and Callaghan (West)

FEDERAL DRUG ADMINISTRATION HEARING
APRIL 23, 2002

STATEMENT

1. PERSONAL INTRODUCTION

I am William W. Brown, currently 69 years of age, from Columbus, Ohio. My address is 2999 East Dublin-Granville Road, Columbus, Ohio 43231. I have been a practicing attorney in Columbus for forty-two years and a licensed pilot for 35 years and have suffered with Irritable Bowel Syndrome for nearly forty years.

Other than IBS my health is very good: low cholesterol levels, and no prior genetic or personal history of cancer, heart problems, diabetes or stroke.

I was first diagnosed with irritable bowel syndrome in approximately 1963 by a Columbus gastroenterologist who at that time called it a "dumping syndrome" later called spastic colon. His statement was that this was all caused by stress and if you get over the stress you will eliminate the problem.

In the late 1960's a family physician prescribed Lomotil which worked for a while. The dosage had to be increased gradually since the body apparently adapts to it. By the late 1990's it only had moderate effects and only if you were taking four pills at a time. It is well known that the maximum dosage is eight pills per day, and as a pilot I am not allowed to take this medication while flying. Since I used my airplane in business, flying to client conferences in Michigan, Ohio, Washington D.C., Chicago, etc., the non-use of this medication restricted the use of my aircraft.

After a physical examination in the summer of 1999 with a Columbus gastroenterologist he said " Well, you have the same problem you have always had which we now call irritable bowel syndrome. Maybe in ten years we will find a cure and laugh about it".

In October of 1999 I went to Mayo Clinic in Rochester, Minnesota for a complete physical examination which included a colonoscopy. Prior to that time I had every possible test made to determine what the nature of the disease was and what could be done to transform it including dermatological examinations for food sensitivity, H pylori, gall bladder scans and complete blood work-up. In November 1999 Mayo Clinic in Rochester did colon motility testing and determined that motility was far too rapid.

Upon using Alosetron beginning in November of 1999 for six weeks the subsequent colon motility testing was much improved at a reduced rate. During the period that I was taking Alosetron I was able to eat practically anything.

Subsequent to this open label study I was on at Mayo Clinic and after the Alosetron trial was over I was given a prescription for Zofran which was moderately effective until Lotronex was approved in March of 2000. I began taking two tablets per day of Lotronex as soon as it was available on the market and continued until December of 2000, approximately a month after it was recalled. I remained on Zofran from time to time as needed until November 2001 along with occasional doses of Lomotil until November 2001 when I began participation in a Solvey Cilasetron double blind study in Columbus, Ohio. Since that time I have been unable to take any medication for IBS except the study medication which apparently is a placebo since the IBS symptoms are back with a vengeance.

2. EFFECTS OF IBS-D

A. SOCIAL Since suffering with irritable bowel syndrome, many events have been eliminated from our calendar including such things as the symphony, opera, stage and even movies due to the fact that frequently explosive IBS occurs at an unpredictable time and with no warning.

B. TRAVEL Short travel is mandated with IBS, however with Lotronex anything is possible. One has to be aware where all bathrooms are at all times when traveling and consider the frequent need to travel with a complete new set of underwear, medication, etc., travel is too difficult.

C. WORK When I am trying cases I am most often take two briefcases to the court room. One contains underwear, medication, wash cloths and other things necessary in the event an explosive diarrhea situation occurs. In addition over the last forty year I have frequently had to cancel or interrupt client conferences due to explosive diarrhea or just being too exhausted after a serious bout of diarrhea for several days.

D. EATING HABITS I must avoid many foods including the following: Herbs, salads, sauces, ethnic foods, wine, blue cheese, bearnaise sauce, bacon, lettuce, tomatoes, cabbages, rare beef, and many other foods. Even foods cooked with wine are an automatic problem. I might add that this gets worse as you get older.

On two occasions, business golf outings were interrupted with episodes of explosive diarrhea. No bathrooms were available, only bushes and woods. Needless to say this was extremely embarrassing for both me and the clients.

3. **AFTER LOTRONEX** Lotronex is almost a "miracle cure" for me. I was able to travel anywhere as long as I had my supply of Lotronex with me. In fact my wife and I were able to make an around the world trip to places not normally visited such as Easter Island, Papua New Guinea, Cambodia, India, Oman, and even Tanzania without any effects of IBS. This was a three week trip in all third world countries which have very little medicine available or clean bathrooms.

In addition I have been able to eat almost anything including the worst offenses to me which are wine, herbs, tomatoes and blue cheese.

I have never experienced any side effects with the use of Lotronex including constipation. This is also been true with my use of Zofran although Zofran is not nearly as effective as Lotronex. Nothing works for me except Lotronex. In the past and over the years I have tried Metamucil, Immodium, Levbid, Calcium and Lomotil. None of these have ever worked for me at all with the exception of Lomotil to some extent.

IMAGE

Ever since man discovered fire he realized the risk of getting burned. The risk was acceptable however in order that he might have heat, light, and be able to cook his meals, and he accepted that risk.

Until nearly one hundred years ago our government maintains that attitude - that man must accept certain risks, and the government's job was not ensure man against all risks.

Slowly, over the last hundred years our government has told us, first, that fire must licensed. Next we were told there were only certain people who could light fires, and then only in certain places fire could be made. There were also laws passed which created fines and imprisonment for violating fire laws.

At the turn of the 21st century our government is now saying the risk of using fire is too great - live in the cold and the dark - the risks of getting burned are too great to allow the risk to continue, plus someone might sue us.

4. **RISK MANAGEMENT** I have read the complete 247 page transcript of the June 27, 2000 Advisory Committee and understand the FDA's concerns on postmarketing of Lotronex. It would appear that Glaxo Smith Kline had already developed an aggressive and responsible postmarketing plan, as outlined by Dr. Elizabeth Anderson and J.S Hull, which included an FDA approved observational cohort design study of 10,000 Lotronex users, constipation management study and communication program. The communications program itself is as thorough as possible and needs no re-explanation.

Dr. Michael Camilleri of Mayo Clinic in an article written for the Gastroenterology Journal last year addressed this issue and discussed what he called the "Exquisite Dilemma" of the risk/benefit issue. **"Unfortunately, withdrawing a drug while saving some individuals from a serious adverse effect, may deprive others of the only agent able to relieve their suffering."**

There is currently no effective postmarketing surveillance on most drugs to enable the manufacturer or the FDA to more clearly determine drug efficacy or safety. In the case of Lotronex, I would be willing to participate in a reporting system. The problem seems to be that physicians do not make reports and patients do not always follow advice. What methods may be available to ensure the safety of Lotronex? A number of ideas have been advanced:

a) Compassionate Use: While the FDA may permit a limited use for certain persons, it as been reported that most pharmaceutical companies including Glaxo SmithKline are not willing to commit to that approach.

b) Restrict dispensation of the drug to gastroenterologists. This is overly restrictive as many family physicians and general practitioners are more knowledgeable about Lotronex than specialists. In my own case, my family physician has 20%, or four of his staff who are affected with IBS-D and has read all of the literature available on IBS and Lotronex. In addition many patients may live in small communities with no access to a gastroenterologist.

c) Waivers: Most of us who were greatly benefited by Lotronex would be willing to sign waivers of non-liability in favor of the FDA and the pharmaceutical company. This, however does not address postmarketing concerns of the FDA.

d) Warning Labels: Better warning labels probably are ineffective. The patients seldom read them, or feel they do not apply to them.

e) Physician Education: Perhaps the FDA can create a class of physicians who are permitted to write these prescriptions who have, or have agreed to certain minimal requirements in Lotronex education, and who have agreed to monitor closely the patient's use of Lotronex; possibly set minimum guidelines on prescriptions, such as quarterly physician/patient visits, colonoscopy every 3-5 years, or annual physical examinations, all to be reported by the physician to the FDA.

5. GENDER AND AGE DISCRIMINATION

The FDA originally approved Lotronex for women only. Several writers have indicated men were not benefited from the drug. This assertion is false, as you can see by the number of men speaking today. It would appear from the historical position that women may suffer more from IBS than men. It is also true that there are many more women undergoing studies than men for at least two reasons: The first is that a women's physical makeup is far more complex than men. Second, probably is that men are just plain not as interested in study programs.

In addition there have been a number of articles indicating that IBS generally diminishes with age. This is also not true. Certainly my IBS is ten times worse at age 69 as it was at 59. To my knowledge, there have been no studies that have quantified this position.

I urge you to make Lotronex available for men, as well as women. Postmarketing surveys to be done by Glaxo Smith Kline can support this position.

6. CONCLUSION

My position is that the job of the FDA is to ensure the safety and efficacy of any drug but not to ensure that no one is at risk by taking any drug which would include aspirin. All drug manufacturers including Glaxo Smith Kline are entitled to sell their products at a reasonable profit after approval of the FDA so long as there are reasonable warning labels. No pharmaceutical company is guaranteeing in any way that nobody is at risk in taking their medication. That is why we have warning labels.

It is the responsibility of the patient and the local physician to whom the patient goes to ensure the medication is being taken properly. My feeling is in many cases the patient feels that if they were prescribed one pill then two is twice is good and everybody knows this is just not the case. In addition it is the patient's responsibility to monitor their own health not run to the attorney to sue the manufacturer because they were negligent themselves in using the medication.

Perhaps there needs to be more physician education regarding the prescription of Lotronex. I have a son who is a drug representative for Eli Lilly and previous to that with Upjohn Pharmaceuticals. This has been his chosen career for the last ten years and he tells me it is very difficult due to the schedules of the physicians to allow him to "detail" the individual drugs which he is representing. In his case it is a diabetes medication. Therefore, I would urge that Lotronex be brought back as soon as possible and be allowed to be dispensed by any physician and that the physicians be educated in the proper use of Lotronex with their patients. This should require a closer relationship between the doctor and the patient although even the doctor is not going to be able to monitor the patient's use of the prescription. The absence of treatment is a violation of the Hippocratic oath in and of itself.

Finally considering the number of physicians who have prescribed Lotronex accurately and successfully and the number of patients whose quality of life has been so dramatically improved it would appear unreasonable to eliminate this medication. The medical standard has always been "first do no harm". Since many of you on this advisory panel are physicians it would appear to me that it almost amounts to medical malpractice to deny those of us who were so benefited from Lotronex, the use of this medication.

THE OHIO STATE UNIVERSITY
HEALTH SCIENCES CENTER

College of Medicine and Public Health
Department of Physiology and Cell Biology

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Phone: (614) 292-5448
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November 6, 2000

Jane Henney, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Henney:

My name is Jackie D. Wood. My title is Professor of Physiology & Cell Biology and Internal Medicine in the College of Medicine and Public Health of The Ohio State University. I served as Chair of the Department of Physiology in the University of Nevada School of Medicine from '79 to '85 and Chair of the Department of Physiology at Ohio State from '85 to '97. My Ph.D. is from the Department of Physiology and Biophysics, University of Illinois, Urbana in 1969. I was the first to record nerve impulses from single neurons in the enteric nervous system and this became the topic for my dissertation. My entire career has been oriented to investigation of the neurophysiology of the enteric nervous system. I coined the tongue-in-cheek expression, brain-in-the-gut in one of my 143 peer-reviewed publications on the enteric nervous system. My research on the enteric nervous system has been funded continuously by no less than two grants from the NIH each year since 1971.

I was enlisted as a consultant by the GlaxoWellcome Company for the development of their drug alosetron (Lotronex) because alosetron is a highly selective antagonist for the 5-hydroxytryptamine 5-HT3 receptor subtype and my laboratory group was the first to report in 1979 the excitatory actions of 5-HT on impulse firing in enteric neurons.

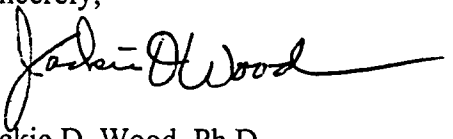
My purpose in writing is to comment on the adverse publicity the drug has received in the popular press as a result of an unproven connection of the drug with ischemic colitis as a side effect. We know precisely how the drug works as an enteric neuromodulator. Both secretomotor neurons in the intestinal submucous plexus and spinal sensory afferents from both small and large bowel express excitatory 5-HT3 receptors. The receptors at these sites are exposed to relatively high levels of 5-HT following its release from enterochromaffin cells in the mucosa and certain inflammatory/immune cells. Alosetron, like other selective 5-HT3 blocking drugs presently on the market, acts to suppress the action of 5-HT at these sites. This action at secretomotor neurons accounts for efficacy in the treatment of diarrhea. Action at the 5-HT3 receptors on spinal afferents accounts for efficacy in treatment of abdominal pain

and discomfort. Alosetron is more effective than other 5-HT3 antagonists because it binds more tightly to the receptor and is therefore effective in lower doses with a longer pharmacokinetic half-life.

Alosetron is the only drug presently available with proven efficacy in the treatment of the diarrhea predominant form of the irritable bowel syndrome in women. My concern is that the drug is in danger of being removed from the market based on unfounded contention that ischemic colitis can result from its actions in the gut. Ischemic colitis is a large vessel disease associated with a number of systemic vascular conditions (eg., clotting disorders and atherosclerosis). We know very well the mechanism of action of alosetron in the gut. The actions are neural at the level of the enteric nervous system – there is no evidence for any actions on the intestinal vasculature. The primary side effect of alosetron is constipation, that can result from blocking the excitatory action of 5-HT on the secretomotor innervation of the intestinal crypts. My colleagues in gastroenterology and primary care generally agree that the constipation is a readily manageable event if it should occur in their patients.

Given that we know of no scientific basis for the drug to produce intestinal ischemia and based on the positive outcomes of the clinical trials, as well as a growing body of anecdotal accounts of efficacy, my opinion is that consideration for denial of access to the drug for a significant patient population is unjustified.

Sincerely,



Jackie D. Wood, Ph.D.
Professor of Physiology & Cell Biology
And Professor of Internal Medicine
Chairman Emeritus, Department of Physiology

Comment From the Editors

Postapproval Drug Surveillance and the First Principle of Medicine

The overarching importance of the first principle of medicine—first, do no harm—is self-evident, but its application is often more complicated than anticipated. Although the obligation to avoid treatments that have little chance of benefiting the patient but confer risk of serious injury is straightforward, medicine seldom offers black and white choices but rather frequently serves them up in shades of gray. Thus benefits and risks need to be weighed to know how best to advise the patient. Most importantly, it is often clear in daily practice that the failure to act or accept the risks of adverse effects of a treatment can also lead to harm. For the gastroenterologist, this may be best illustrated by the issues inherent to soliciting informed consent for screening colonoscopy; the small risk of perforation or other complication is real, but not performing the test may result in failure to diagnose a polyp that might ultimately prove fatal.

The paradoxes of the first principle of medicine apparent in its application to individual patients are also present in its application to large patient populations. In our judgment, this is exemplified in the efforts of the Food and Drug Administration (FDA) to ensure the safety of drugs. The FDA is charged with evaluating drugs developed by pharmaceutical companies for their safety and efficacy for the benefit of the public. Fulfilling these responsibilities has become more complicated in recent years for a number of reasons. The latter include an increased sensitivity to the economic impact of newly approved medications. In the postgenome era, drug development will also be refined through better definition of patient subsets more likely on a genetic basis to respond (perhaps because of a specific isoform of the drug target) or develop toxicity (possibly related to a particular variant drug metabolizing enzyme) when given an agent. It is likely that FDA will need to incorporate these additional perspectives into their evaluation of new therapeutics before granting approval.

Notwithstanding these additional challenges, the FDA has rigorous approval processes in place. However, the mechanisms for monitoring drug safety after approval suffer from a number of weaknesses. This function is essential; the full safety profile of a drug only really becomes clear after several thousands of patients have been treated rather than the hundreds who may have been included in Phase III studies that formed the basis for initial approval. Postmarketing surveillance is necessary but requires enormous effort given the large number of patients who may be treated and the increasing number of medications surveyed.

We applaud the postmarketing monitoring that is required by the regulatory authorities in the recommendations typically provided during the final approval of a medication. However, despite the large effort committed to this goal, it falls short of comprehensive and thorough surveillance. Some of the limits are obvious: for the most part, report of adverse effects by physicians after approval is voluntary. Moreover, the reporting physicians are left to make judgements about the relationship between the adverse event and the medications within somewhat arbitrary and limited categories. Just as importantly, the standards for diagnosis and documentation of the nature of the adverse event are not uniform and are subject to physician error. With these limits, determination of the true risk and benefit ratio is inherently problematic when issues of unexpected toxicity raise questions about continued approval.

In noting these potential pitfalls, one might ask: what is the harm (other than possibly to the economic interests of a pharmaceutical company) in withdrawing a medication? Primum non nocere? Unfortunately, withdrawing a drug, while saving some individuals from a serious adverse effect, may deprive others of the only agent able to relieve their suffering. This exquisite dilemma is highlighted by the unfolding of events leading to withdrawal of cisapride from the market. This agent had been approved for the treatment of nocturnal heartburn. Much evidence had subsequently suggested its efficacy in the treatment of various motility disorders of the upper gastrointestinal tract. However, reports of significant cardiac arrhythmias, some fatal, led to this medication being, for all practical purposes, removed from the market (though it should be noted, the possibility of obtaining it through an individual IND provides a residual avenue of access with a very high threshold). However, it seems that many of the adverse events may have occurred in the context of use of inappropriate, not evidence-based, doses for unapproved indications and without regard to warnings of significant drug interactions. Although severe restriction protects those individuals for whom the risk could not be justified by the limited benefit, the consequences for other patients with a legitimate need for the medication have been significant. Withdrawal has been especially devastating for many patients with gastroparesis and pseudo-obstruction for whom cisapride had proven effective. Long-term studies had shown that many severely affected patients were able to remain off parenteral nutrition, out of hospital, and avoid dehydration and other complications. Will alosetron be another case in point?

In the final analysis, it is appropriate that the burden of proof rests on the drug manufacturer to demonstrate convincingly the lack of a scientific basis for the relationship between the actions of their product and an apparent complication. The manufacturer should also provide as assessment of the frequency of that event in an untreated matched relevant population. However, the interest of physicians and the FDA must be a balanced one: to develop means that provide comprehensive and accurate surveillance of postapproval drug use but to incorporate the totality of the interests of patients. The latter includes full explication of the risk of adverse effects, but also the potential adverse consequences for some patients in withdrawing an agent. Gastroenterologists have a responsibility to provide expert input for a reasoned assessment of both sides of that equation. The first principle of medicine demands it.

MICHAEL CAMILLERI, M.D.
Associate Editor
DANIEL K. PODOLSKY, M.D.
Editor

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Review Article

Current Concepts

THE IRRITABLE BOWEL SYNDROME

BRENDA J. HORWITZ, M.D., AND ROBERT S. FISHER, M.D.

IN 1849, Cumming[1] said of the irritable bowel syndrome, "The bowels are at one time constipated, another lax, in the same person. How the disease has two such different symptoms I do not profess to explain." Over the years, the unexplained gastrointestinal symptoms of the irritable bowel syndrome have been described in various terms, including mucous colitis, spastic colitis, nervous colon, and irritable colon. The irritable bowel syndrome and nonulcer dyspepsia are the most common functional gastrointestinal disorders.

The irritable bowel syndrome is defined on the basis of the recently modified Rome criteria as the presence for at least 12 weeks (not necessarily consecutive) in the preceding 12 months of abdominal discomfort or pain that cannot be explained by structural or biochemical abnormalities and that has at least two of the following three features: pain is relieved with defecation, its onset is associated with a change in the frequency of bowel movements (diarrhea or constipation), or its onset is associated with a change in the form of the stool (loose, watery, or pellet-like).[2] The syndrome can be divided into four subcategories according to whether the predominant symptom is abdominal pain, diarrhea, constipation, or constipation alternating with diarrhea.

EPIDEMIOLOGIC FEATURES

Approximately 15 percent of U.S. adults report symptoms that are consistent with the diagnosis of the irritable bowel syndrome[3]; the disease affects three times as many women as men. Whether this difference reflects a true predominance of the disorder among women or merely the fact that women are more likely to seek medical care has not been determined. The irritable bowel syndrome is the most common diagnosis made by gastroenterologists in the United States[4] and accounts for 12 percent of visits to primary care providers.[5] It is estimated that only 25 percent of persons with this condition seek medical care for it, and studies suggest that those who seek care are more likely to have behavioral and psychiatric problems than are those who do not seek care.[6] In addition, patients with a diagnosis of the irritable bowel syndrome are at increased risk for other, nongastrointestinal functional disorders such as fibromyalgia and interstitial cystitis.[7,8] The irritable bowel syndrome accounts for an estimated $8 billion in direct medical costs and $25 billion in indirect costs annually in the United States.[9]

From the Gastroenterology Section and the Functional Gastrointestinal Diseases Center, Temple University School of Medicine, Philadelphia. Address reprint requests to Dr. Fisher at the Gastroenterology Section, Temple University Hospital, 3401 N. Broad St., Philadelphia, PA 19140.

PATHOPHYSIOLOGIC FEATURES

Altered bowel motility, visceral hypersensitivity, psychosocial factors, an imbalance in neurotransmitters, and infection have all been proposed as playing a part in the development of the irritable bowel syndrome (Fig. 1).

Altered Bowel Motility

Over the past 50 years, alterations in the contractility of the colon and small bowel have been described in patients with the irritable bowel syndrome. Psychological or physical stress[10] and ingestion of food[11] may alter the contractility of the colon. Abnormal motility of the small intestine during fasting, such as loss of the migrating motor complex[12] and the presence of both discrete, clustered contractions and prolonged, propagated contractions,[13] has been described in patients with the irritable bowel syndrome. In addition, an exaggerated contractile response to a high-fat meal has been reported.[13] Pain is more frequently associated with irregular motor activity of the small intestine in patients with this syndrome than in normal controls or patients with inflammatory bowel disease.[12]

Visceral Hypersensitivity

Balloon-distention studies of the rectosigmoid[14] and the ileum[15] have shown that patients with the irritable bowel syndrome experience pain and bloating at balloon volumes and pressures that are significantly lower than those that induce pain in control subjects, a phenomenon referred to as visceral hypersensitivity. One possible explanation is that the sensitivity of receptors in the viscus is altered through the recruitment of silent nociceptors in response to ischemia, distention, intraluminal contents, infection, or psychiatric factors.

There may be increased excitability of the neurons in the dorsal horn of the spinal cord, an area rich in neurotransmitters such as catecholamines and serotonin. Centrally, there may be differences in the way

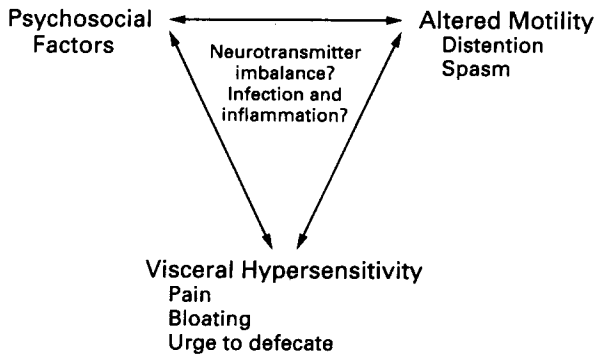

Figure 1. Pathophysiologic Factors in the Development of the Irritable Bowel Syndrome.

The double-headed arrows indicate an interaction.

the brain modulates afferent signals from the dorsal-horn neurons through the ascending pathways. Functional magnetic resonance imaging[16,17] and positron-emission tomography[18,19] of the brain show different levels of activation in the thalamus and the anterior cingulate cortex after balloon distention of the rectum in patients with the irritable bowel syndrome, as compared with normal subjects.

These findings, although controversial, suggest a primary central defect of visceral pain processing. Some authors have suggested that hypervigilance rather than true visceral hypersensitivity may be responsible for the low pain threshold in patients with the irritable bowel syndrome.

Psychosocial Factors

Psychological stress can alter motor function in the small bowel[11] and colon,[20] both in normal subjects and in patients with the irritable bowel syndrome. Up to 60 percent of patients seen at referral centers have psychiatric symptoms such as somatization, depression, and anxiety, and patients with a diagnosis of the irritable bowel syndrome are more likely to have these symptoms than are persons who have never sought medical care for bowel problems.[21,22] When present, psychiatric disturbances influence overall use of health care services and the ability to cope with symptoms. The presence or absence of a history of abuse in childhood (sexual, physical, or both) is correlated with the severity of symptoms in patients with the irritable bowel syndrome.[23] It has even been proposed that experiences early in life may affect the central nervous system and confer a predisposition to a state of hypervigilance.

Neurotransmitter Imbalance

Recent studies have suggested that neurotransmitters are involved in the pathogenesis of the irritable bowel syndrome. Five percent of serotonin is located in the central nervous system, and the remaining 95 percent is in the gastrointestinal tract, within enterochromaffin cells, neurons, mast cells, and smooth-muscle cells. When released by enterochromaffin cells, serotonin stimulates extrinsic vagal afferent nerve fibers and intrinsic enteric afferent nerve fibers, resulting in such physiological responses as intestinal secretion and the peristaltic reflex and in such symptoms as nausea, vomiting, abdominal pain, and bloating.[24] Preliminary evidence suggests that patients with the irritable bowel syndrome have increased serotonin levels in plasma and in the rectosigmoid colon.[25,26]

Other neurotransmitters that may have an important role in functional gastrointestinal disorders include calcitonin gene–related peptide, acetylcholine, substance P, pituitary adenylate cyclase–activating polypeptide, nitric oxide, and vasoactive intestinal peptide. These neurotransmitters may provide links not only between bowel contractility and visceral sensitivity, but also between the enteric and central nervous systems.

Infection and Inflammation

There is compelling evidence that inflammation of the enteric mucosa or neural plexuses initiates or contributes to symptoms associated with irritable bowel syndrome.[27-29] Mucosal inflammatory cytokines may activate peripheral sensitization or hypermotility. Gwee et al. reported that in patients with infectious enteritis, the presence of hypochondriasis and stressful life events at the time of the acute infection predicted the subsequent development of the irritable bowel syndrome.[30] To date, no single conceptual model can explain all cases of the syndrome.

DIAGNOSIS

After a complete history has been obtained, all patients with lower gastrointestinal tract symptoms should undergo a complete physical examination and laboratory testing, including a complete blood count, blood-chemistry tests, liver-function tests, and measurement of thyrotropin. The diagnosis of the irritable bowel syndrome is suggested when a patient's symptoms meet the Rome criteria. In the majority of cases, there are no abnormalities on physical examination or laboratory testing and there are no findings suggestive of a structural disorder — so-called alarm symptoms. Therefore, the irritable bowel syndrome can be reasonably diagnosed on the basis of flexible sigmoidoscopy alone, in patients who are less than 50 years old, or colonoscopy, in those who are 50 or older; barium enema and flexible sigmoidoscopy are often substituted for colonoscopy. In patients with diarrhea, a biopsy specimen should be obtained from the mucosa of the descending colon to rule out microscopic colitis.

If there are abnormalities on physical examination or laboratory testing or if an alarm symptom is present,

the irritable bowel syndrome is a diagnosis of exclusion after reasonable diagnostic testing has been performed, such as colonoscopy, computed tomographic scanning of the abdomen and pelvis, and radiographic evaluation of the small intestine. Alarm symptoms include evidence of gastrointestinal bleeding such as occult blood in the stool, rectal bleeding, or anemia; anorexia or weight loss; fever; persistent diarrhea causing dehydration; severe constipation or fecal impaction; a family history of gastrointestinal cancer, inflammatory bowel disease, or celiac sprue; and the onset of symptoms at the age of at least 50 years. In 1985, the American College of Physicians recommended the use of alarm symptoms to guide treatment[31]; however, the validity of this approach has never been established in rigorous, randomized, prospective clinical studies.

A number of structural or metabolic disorders that are responsive to specific treatment cause symptoms similar to those of the irritable bowel syndrome. Lactase deficiency is a common culprit. Other such disorders include cancer of the colon, diverticulitis, mechanical obstruction of the colon or small intestine, inflammatory bowel disease, enteric infection, ischemia, maldigestion or malabsorption, and endometriosis (suggested by the presence of pelvic pain at the time of the menstrual period). In the absence of alarm symptoms, the presence of one of these structural or metabolic disorders is very unlikely.

TABLE 1. SYMPTOM-GUIDED TREATMENT OF THE IRRITABLE BOWEL SYNDROME.*

Pain predominant
Change in diet
Anticholinergic agent
Nitrate
Tricyclic compound
Visceral antinociceptive agent (alosetron† or tegaserod‡)
Selective serotonin-reuptake inhibitor
Nonsteroidal antiinflammatory drug
Opioid
Diarrhea predominant
Change in diet
Loperamide
Diphenoxylate
Cholestyramine
Alosetron†
Constipation predominant
Change in diet
Osmotic laxative
Other laxatives
5-HT_4–receptor agonist (tegaserod‡ or prucalopride§)

*None of the drugs listed in this table are approved by the Food and Drug Administration (FDA) for treatment of the irritable bowel syndrome. 5-HT_4 denotes 5-hydroxytryptamine$_4$.

†The FDA initially approved this use of the drug but subsequently withdrew its approval.

‡An application for approval has been submitted to the FDA.

§The FDA has suspended its investigation of this use of the drug (see text).

TREATMENT

Whether the irritable bowel syndrome is diagnosed on the basis of the history, physical examination, and laboratory tests or after extensive testing (because of the presence of an alarm symptom), the establishment of trust in the physician–patient relationship should be given a high priority in order to maximize the efficacy of treatment and minimize "doctor shopping." A diary of food intake and symptoms can be useful in identifying foods that may be associated with symptoms of the irritable bowel syndrome. Patients often report an exacerbation of symptoms after the consumption of certain foods. Some patients benefit from avoiding or limiting their intake of caffeine, alcohol, fatty foods, gas-producing vegetables, or products containing sorbitol, such as sugarless gum and dietetic candy. The avoidance of constipating foods and the addition of 20 to 30 g of fiber per day either in the diet or in the form of supplements such as bran, polycarbophil, or a psyllium derivative may help relieve constipation[32-35] and may occasionally improve diarrhea.

A rational approach to treating the irritable bowel syndrome uses the patient's symptoms as a guide (Table 1). For patients in whom the disorder is manifested predominantly as abdominal pain, a variety of medications have been used, and several new agents are under development. Antispasmodic agents may reduce abdominal pain or bloating through anticholinergic pathways; in refractory cases, nitrates are occasionally useful for direct relaxation of smooth muscles. A recent meta-analysis suggested the effectiveness of antispasmodic agents and tricyclic compounds in treating selected patients with the irritable bowel syndrome.[36] Unfortunately, many of these agents are not available in the United States, and large-scale, stand-alone studies have not been performed. Small studies have shown that tricyclic compounds in low doses relieve unexplained abdominal pain.[37] Side effects — sedation, dry mouth and eyes, and weight gain — limit the use of primary tricyclic amines. Secondary tricyclic amines such as nortriptyline and desipramine may be less likely to have side effects.[38]

Despite speculation that 5-hydroxytryptamine (5-HT), or serotonin, receptors may be involved in the pathogenesis of the irritable bowel syndrome, the results of treatment with selective serotonin-reuptake inhibitors have been disappointing. Nevertheless, serotonin has been implicated in the modulation of visceral nociception, especially through the 5-HT_3 and 5-HT_4 pathways. Two new agents — alosetron, a 5-HT_3–receptor antagonist, and tegaserod, a 5-HT_4 agonist — have been shown to diminish visceral sensitivity to rectal distention in women who

have diarrhea as the predominant symptom of the irritable bowel syndrome and in those who have constipation as the predominant symptom, respectively.[39,40] Fedotozine, a kappa-opioid agonist,[41] has shown promise as a visceral antinociceptive agent, and other kappa-opioid agonists are being developed. Finally, in some patients who have abdominal pain that is refractory to all these therapeutic agents, treatment with classic analgesics such as nonsteroidal antiinflammatory agents (perhaps with an initial trial of a cyclooxygenase-2 inhibitor) or, in extreme cases, opioid analogues may control the pain and improve the quality of life. The addictive potential of opioid analogues makes them the last choice for long-term therapy.

For patients in whom diarrhea is the predominant manifestation of the irritable bowel syndrome, classic antidiarrheal agents such as loperamide[42] and diphenoxylate may help decrease the frequency of bowel movements and improve the consistency of stool. In a study of women with this form of the irritable bowel syndrome, alosetron prolonged colonic transit, reduced the frequency of bowel movements and the urge to defecate, improved the consistency of stool, and decreased abdominal pain.[43] However, this drug has been removed from the market because of side effects such as severe constipation, ischemic colitis, and bowel perforation. In cases of diarrhea that cannot be controlled, cholestyramine has been used to bind bile acids that may be responsible for increased secretion and decreased absorption of water in the colon.[44] In some refractory cases, a short course of antibiotics may reduce the diarrhea, presumably by altering the intestinal flora.[45]

For patients in whom constipation is the predominant manifestation of the irritable bowel syndrome, consumption of fiber may alleviate constipation and related symptoms such as abdominal pain, tenesmus, and dyschezia.[32] Constipation can also be safely treated with osmotic laxatives such as nonabsorbable carbohydrates (lactulose and sorbitol), milk of magnesia or magnesium citrate, or a polyethylene glycol solution. Two new classes of compounds, aminoguanidine indoles such as tegaserod and benzofurans such as prucalopride, act specifically on 5-HT_4 receptors. These agents shorten the transit time in the colon and small intestine, increase the frequency of bowel movements, and increase the softness of stools.[46-49] Studies of prucalopride have been suspended because of concern about tumorigenic effects in animals. Derivatives of anthraquinones (senna and cascara), which act as strong laxatives, may be used as a last resort, but their use is limited by the frequent development of tachyphylaxis. The question of whether anthraquinones and their derivatives damage the enteric nervous system has not been resolved.

Although many pharmacologic agents have been used to treat the irritable bowel syndrome, few have been tested in controlled, double-blind studies with adequate statistical power. The doses of some commonly used agents are shown in Table 2.

TABLE 2. DOSAGE GUIDELINES FOR DRUGS COMMONLY USED TO TREAT THE IRRITABLE BOWEL SYNDROME.

DRUG	DOSE
Anticholinergic agents	
Dicyclomine hydrochloride	20 mg every 6 hr; can be increased to 40 mg every 6 hr if tolerated
Hyoscyamine sulfate	0.125–0.25 mg sublingually every 4 hr (0.375-mg extended-relief tablets: 1 or 2 tablets every 12 hr)
Antidiarrheal agents	
Loperamide	4 mg/day initially, with a maintenance dose of 4–8 mg/day, in a single or divided dose
Diphenoxylate (2.5 mg) plus atropine sulfate (0.025 mg)	2 tablets 4 times a day
Cholestyramine resin	1 packet (9 g) mixed with fluid and taken once or twice a day
Osmotic laxatives	
Lactulose	10 mg/15 ml of syrup; 15–30 ml/day (usual dose), up to 60 ml/day
Polyethylene glycol solution	17 g dissolved in 240 ml (8 oz) of water, taken daily
Tricyclic compounds	
Amitriptyline	25–75 mg/day
Nortriptyline	25–75 mg/day
Desipramine	25–75 mg/day

The interaction between psychosocial factors and the genesis of all forms of the irritable bowel syndrome is poorly understood. The most provocative observations in this respect are that persons with the syndrome who seek care are those in whom the syndrome is accompanied by a psychiatric disorder and that the syndrome may develop in patients who have both infectious gastroenteritis and a psychiatric disorder. The potential benefits of supportive therapy, relaxation exercises, hypnosis, cognitive behavioral therapy, and psychodynamic interpersonal psychotherapy are well recognized.[50]

The irritable bowel syndrome is a common disorder that has a pronounced effect on the quality of life and that accounts for a large proportion of health care costs. Common pitfalls in diagnosing and treating this disorder include unnecessary repetition of tests, failure to establish trust in the physician–patient relationship, and failure to provide the patient with realistic expectations regarding the efficacy of medications. A concise diagnostic evaluation and prompt institution of symptom-guided therapy can help alleviate the pain and suffering experienced by patients with the irritable bowel syndrome.

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